Invento Dearch

Kolker 10/791,434

28/02/2005

## => d ibib abs ind hitstr 15 1-1

ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:521523 HCAPLUS

DOCUMENT NUMBER: 137:73273

Adrenergic receptor ligand-neurotoxin conjugates and TITLE:

methods for treating pain

Gil, Daniel W.; Aoki, Kei Roger INVENTOR(S):

PATENT ASSIGNEE(S): Allergan Sales, Inc., USA SOURCE: PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. |     |       | KIND DATE |      |     | APPLICATION NO. |           |      |      |                |      | DATE  |      |     |            |          |      |     |  |
|------------|-----|-------|-----------|------|-----|-----------------|-----------|------|------|----------------|------|-------|------|-----|------------|----------|------|-----|--|
|            |     |       |           |      |     |                 |           |      |      |                |      |       |      |     |            |          |      |     |  |
|            | WO  | 20020 | 0531'     | 77   |     | A2              | A2 200207 |      |      | 1              | WO 2 | 001-1 | US48 | 651 |            | 20011214 |      |     |  |
|            | WO  | 2002  | 0531      | 77   |     | A3              |           | 2003 | 0918 |                |      |       |      |     |            |          |      |     |  |
|            |     | W:    | ΑE,       | AG,  | AL, | AM,             | ΑT,       | AU,  | AZ,  | BA,            | BB,  | BG,   | BR,  | BY, | ΒZ,        | CA,      | CH,  | CN, |  |
|            |     |       | CO,       | CR,  | CU, | CZ,             | DE,       | DK,  | DM,  | DZ,            | EC,  | EE,   | ES,  | FI, | GB,        | GD,      | GE,  | GH, |  |
|            |     |       | GM,       | HR,  | HU, | ID,             | IL,       | IN,  | IS,  | JP,            | KE,  | KG,   | KP,  | KR, | KZ,        | LC,      | LK,  | LR, |  |
|            |     |       | LS,       | LT,  | LU, | LV,             | MA,       | MD,  | MG,  | MK,            | MN,  | MW,   | MX,  | MZ, | NO,        | NZ,      | PL,  | PT, |  |
|            |     |       | RO,       | RU,  | SD, | SE,             | SG,       | SI,  | SK,  | SL,            | TJ,  | TM,   | TR,  | TT, | TZ,        | UA,      | UG,  | UZ, |  |
|            |     |       | VN,       | YU,  | ZA, | ZW              | •         | •    | ·    | •              | •    | ,     |      |     | •          | ·        | •    |     |  |
|            |     | RW:   | GH,       | GM,  | KE, | LS,             | MW,       | MZ,  | SD,  | SL,            | SZ,  | TZ,   | UG,  | ZM, | ZW,        | AM,      | AZ,  | BY, |  |
|            |     |       | -         | -    |     | -               | -         | TM,  | -    |                | -    | -     | -    | -   | -          |          | -    |     |  |
|            |     |       |           |      |     |                 |           | NL,  |      |                |      |       |      |     |            |          |      |     |  |
|            |     |       | GN,       | GQ,  | GW, | ML,             | MR,       | NE,  | SN,  | TD,            | TG   |       | ·    | ·   | ·          |          |      |     |  |
|            | US  | 6787  | 517       | -    | •   | В1              | -         | 2004 | 0907 | 1              | US 2 | 000-  | 7510 | 53  |            | 2        | 0001 | 229 |  |
|            | CA  | 24333 | 332       |      |     | AA              |           |      |      |                |      |       |      |     |            |          |      |     |  |
|            | ΕP  | 1363  | 674       |      |     | A2              |           | 2003 | 1126 | 1              | EP 2 | 001-  | 9902 | 12  |            | 2        | 0011 | 214 |  |
|            |     | R:    | AT,       | BE,  | CH, | DE,             | DK,       | ES,  | FR,  | GB,            | GR,  | IT,   | LI,  | LU, | NL,        | SE,      | MC,  | PT, |  |
|            |     |       | IE,       | SI,  | LT, | LV,             | FI,       | RO,  | MK,  | CY,            | AL,  | TR    | •    | -   | •          | -        |      |     |  |
|            | US  | 2004  | 1465      | 32   |     | A1              | ·         | 2004 | 0729 | . 1            | ປຣ 2 | 004-  | 7914 | 34  |            | 2        | 0040 | 301 |  |
| PRIO       | RIT | APPI  | LN.       | INFO | . : |                 |           |      |      | US 2000-751053 |      |       |      | 7   | A 20001229 |          |      |     |  |
|            |     |       |           |      |     |                 |           |      |      |                |      | 001-1 |      |     |            |          | 0011 |     |  |
|            |     |       |           |      |     |                 |           |      |      |                |      |       |      |     |            |          |      |     |  |

OTHER SOURCE(S): MARPAT 137:73273

Agents for treating pain, methods for producing the agents, and methods for treating pain by administration to a patient of a therapeutically effective amount of the agent, are disclosed. The agent may include a clostridial neurotoxin, a fragment or a derivative thereof, attached to a targeting component, wherein the targeting component is selected form a group consisting of compds. which selectively binds at the  $\alpha 2b$  or  $\alpha 2b/\alpha 2c$  adrenergic receptor subtype(s) as compared to other binding sites, e.g. the  $\alpha 2a$  adrenergic receptor subtype.

IC ICM A61K039-00

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

ST adrenergic receptor ligand neurotoxin conjugate analgesic

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study) (MBP (maltose-binding protein), fusion products; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Analgesics

Cytoplasm

Drug delivery systems

Human

Ribosome

(adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Amino acids, biological studies

Gene

Neurotransmitters

RL: BSU (Biological study, unclassified); BIOL (Biological study) (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Antibodies and Immunoglobulins

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Pain

Skin, disease

(allodynia; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Toxins

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(butyricum, conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Pain

(chronic; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Hemocyanins

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Peptides, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Proteins

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (conjugates; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Viscera

(disease, pain; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Drug delivery systems

(injections, i.m.; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Drug delivery systems

(injections, s.c.; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Biological transport

(intracellular; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Drug delivery systems

(intrathecal; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Nerve, disease

(neuropathy, neuropathic pain; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Pain

(referred; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

IT Proteins

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

```
(Biological study); USES (Uses)
        (saporins, conjugates; adrenergic receptor ligand-neurotoxin conjugates
        and methods for treating pain)
IT
     Hydrocarbons, biological studies
     RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
     (Uses)
        (spacer; adrenergic receptor ligand-neurotoxin conjugates and methods
        for treating pain)
IT
     Toxins
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (tetanus, conjugates; adrenergic receptor ligand-neurotoxin conjugates
        and methods for treating pain)
IT
     Disease, animal
        (visceral pain; adrenergic receptor ligand-neurotoxin conjugates and
        methods for treating pain)
IT
     Pain
        (visceral; adrenergic receptor ligand-neurotoxin conjugates and methods
        for treating pain)
IT
     Antigens
     RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
     (Uses)
        (α2b receptor second extracellular loop; adrenergic receptor
        ligand-neurotoxin conjugates and methods for treating pain)
IT
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (α2B; adrenergic receptor ligand-neurotoxin conjugates and
        methods for treating pain)
IT
     Adrenoceptors
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (α2C; adrenergic receptor ligand-neurotoxin conjugates and
        methods for treating pain)
IT
     440645-44-3
     RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological
     study); USES (Uses)
        (adrenergic receptor ligand-neurotoxin conjugates and methods for
        treating pain)
ΙT
     19216-56-9D, Prazosin, conjugates 61290-32-2D,
     conjugates 67339-62-2D, ARC 239, conjugates 81167-16-0D
       Imiloxan, conjugates 93384-43-1D, Botulin A, conjugates
     93384-44-2D, Botulin B, conjugates 93384-46-4D, Botulin
     D, conjugates 93384-47-5D, Botulin E, conjugates
     107231-12-9D, Botulin, conjugates 107231-13-0D, Botulin
     C1, conjugates 107231-15-2D, Botulin F, conjugates
     107231-16-3D, Botulin G, conjugates 366786-91-6D,
     conjugates
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (adrenergic receptor ligand-neurotoxin conjugates and methods for
        treating pain)
     147-85-3, L-Proline, biological studies
     RL: BSU (Biological study, unclassified); BIOL (Biological study)
        (proline-containing polypeptide, spacer; adrenergic receptor
        ligand-neurotoxin conjugates and methods for treating pain)
IT
     440645-44-3
     RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological
     study); USES (Uses)
        (adrenergic receptor ligand-neurotoxin conjugates and methods for
        treating pain)
RN
     440645-44-3 HCAPLUS
```

CN L-Glutamic acid, L-lysylglycyl-L-α-aspartyl-L-glutaminylglycyl-L prolyl-L-glutaminyl-L-prolyl-L-arginylglycyl-L-arginyl-L-prolyl-L glutaminyl-L-cysteinyl-L-lysyl-L-leucyl-L-asparaginyl-L-glutaminyl- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

$$H_2N$$
 $(CH_2)_4$ 
 $NH_2$ 
 $NH_2$ 
 $NH_3$ 
 $NH_4$ 
 $NH_4$ 
 $NH_4$ 
 $NH_5$ 
 $NH_5$ 
 $NH_5$ 

PAGE 1-B

PAGE 1-C

IT 19216-56-9D, Prazosin, conjugates 61290-32-2D,
 conjugates 67339-62-2D, ARC 239, conjugates 81167-16-0D
 , Imiloxan, conjugates 93384-43-1D, Botulin A, conjugates
93384-44-2D, Botulin B, conjugates 93384-46-4D, Botulin
D, conjugates 93384-47-5D, Botulin E, conjugates
107231-12-9D, Botulin, conjugates 107231-13-0D, Botulin
C1, conjugates 107231-15-2D, Botulin F, conjugates
107231-16-3D, Botulin G, conjugates 366786-91-6D,
 conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)
 (adrenergic receptor ligand-neurotoxin conjugates and methods for
 treating pain)

RN 19216-56-9 HCAPLUS

CN Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-(9CI) (CA INDEX NAME)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 67339-62-2 HCAPLUS

CN 1,3(2H,4H)-Isoquinolinedione, 2-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-4,4-dimethyl- (9CI) (CA INDEX NAME)

RN 81167-16-0 HCAPLUS

CN 1H-Imidazole, 2-[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]-1-ethyl- (9CI) (CA INDEX NAME)

RN 93384-43-1 HCAPLUS

CN Botulin A (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 93384-44-2 HCAPLUS

CN Botulin B (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 93384-46-4 HCAPLUS

CN Botulin D (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 93384-47-5 HCAPLUS

CN Botulin E (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 107231-12-9 HCAPLUS

CN Botulin (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 107231-13-0 HCAPLUS

CN Botulin C1 (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 107231-15-2 HCAPLUS

CN Botulin F (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 107231-16-3 HCAPLUS

CN Botulin G (9CI) (CA INDEX NAME)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

IT 147-85-3, L-Proline, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (proline-containing polypeptide, spacer; adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

RN 147-85-3 HCAPLUS

CN L-Proline (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

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=> d his ful
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FILE 'HCAPLUS' ENTERED AT 17:53:20 ON 28 FEB 2005
                                             E GIL DANIEL/AU
                                     42 SEA ABB=ON ("GIL DANIEL"/AU OR "GIL DANIEL W"/AU OR "GIL
L1
                                             DANIEL WALTER"/AU)
                                             E AOKI KEI/AU
                                     71 SEA ABB=ON ("AOKI KEI"/AU OR "AOKI KEI ROGER"/AU)
L_2
                                       1 SEA ABB=ON L1 AND L2
L3
                                             SELECT RN L3 1-1
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                                               OR 107231-16-3/BI OR 147-85-3/BI OR 19216-56-9/BI OR 366786-91
                                             -6/BI OR 440645-44-3/BI OR 61290-32-2/BI OR 67339-62-2/BI OR
                                             81167-16-0/BI OR 93384-43-1/BI OR 93384-44-2/BI OR 93384-46-4/B
                                             I OR 93384-47-5/BI)
              FILE 'HCAPLUS' ENTERED AT 17:54:19 ON 28 FEB 2005
L5
                                       1 SEA ABB=ON L3 AND L4
                                             D IBIB ABS IND HITSTR L5 1-1
                                             ANALYZE L5 1-1 CT :
                                                                                                               22 TERMS
L6
              FILE 'REGISTRY' ENTERED AT 17:56:32 ON 28 FEB 2005
L7
                                           STR
L8
                                       0 SEA SSS SAM L7
L9
                                       0 SEA SSS FUL L7
L10
                                             STR L7
L11
                                       0 SEA SSS SAM L10
                                       0 SEA SSS FUL L10
L12
L13
                                             STR L10
                                       0 SEA SSS SAM L13
L14
L15
                                       0 SEA SSS FUL L13
                                   STR L13

9 SEA SSS SAM L16

161 SEA SSS FUL L16

16/compde from Reg. - Ree d gue 5500 to 500 
L16
L17
L18
                                 161 SEA SSS FUL L16
              FILE 'HCAPLUS' ENTERED AT 18:09:56 ON 28 FEB 2005
L19
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=> d que stat l19
L16 STR

13
S
|||
CH2-NH\(^C-\^\)NH\(^CH2-CH2-OH
6 7 8 9 10 11 12
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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 8

STEREO ATTRIBUTES: NONE

L18 161 SEA FILE=REGISTRY SSS FUL L16

L19 11 SEA FILE=HCAPLUS ABB=ON L18 AND (?PAIN? OR ?ANALGES? OR

?ADRENERG? OR ?ADRENOCEPT?)

## => d ibib abs hitstr l19 1-11

L19 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:331968 HCAPLUS

DOCUMENT NUMBER: 140:332518

TITLE: α2B or α2B/2C Adrenoceptor

agonists for the treatment of neurodegeneration

INVENTOR(S): Wheeler, Larry A.; Gil, Daniel W.; Donello, John E.

PATENT ASSIGNEE(S): Allergan, Inc., USA SOURCE: PCT Int. Appl., 36 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. -----\_\_\_\_\_ \_\_\_\_ \_\_\_\_\_ WO 2004032913 20040422 WO 2003-US31809 A1 20031007 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG US 2003-680879 20031007 US 2004138312 A1 20040715 PRIORITY APPLN. INFO.: US 2002-417049P P 20021008

The invention discloses methods using  $\alpha 2B$  or  $\alpha 2B/2C$ 

adrenoceptor agonists for preventing or retarding the degeneration of neurons. Also disclosed are methods for treating Alzheimer's disease or Parkinson's disease through the administration of selective  $\alpha 2B$ or  $\alpha$ 2B/2C adrenoceptor agonists.

IT 366786-91-6

> RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

( $\alpha$ 2B or  $\alpha$ 2B/2C adrenoceptor agonists for

treatment of neurodegeneration)

RN 366786-91-6 HCAPLUS

Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) CN (CA INDEX NAME)

$$C1$$
  $CH_2-NH-C-NH-CH_2-CH_2-OH$ 

REFERENCE COUNT:

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS 3 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2003:950846 HCAPLUS

DOCUMENT NUMBER:

140:13072

TITLE: Novel methods and compositions for alleviating

pain

INVENTOR(S): Gil, Daniel W.; Donello, John E.

PATENT ASSIGNEE(S): Allergan, Inc., USA SOURCE: PCT Int. Appl., 129 pp.

CODEN: PIXXD2

DOCUMENT TYPE: LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

|      |                   |          |          |                 | APPLICATION NO.             | DATE                |
|------|-------------------|----------|----------|-----------------|-----------------------------|---------------------|
|      |                   |          |          |                 |                             |                     |
|      |                   |          |          | WO 2003-US13057 | 20030423                    |                     |
|      | WO 200309928      |          |          |                 |                             |                     |
|      |                   |          |          |                 | BA, BB, BG, BR, BY          |                     |
|      |                   |          |          |                 | DZ, EC, EE, ES, FI          |                     |
|      |                   |          |          |                 | JP, KE, KG, KP, KR          |                     |
|      |                   |          |          |                 | MK, MN, MW, MX, MZ          |                     |
|      |                   |          |          |                 | SG, SK, SL, TJ, TM          | TN, TR, TT, TZ,     |
|      |                   |          |          |                 | ZA, ZM, ZW                  |                     |
|      |                   |          |          |                 | SL, SZ, TZ, UG, ZM          |                     |
|      |                   |          |          |                 | BE, BG, CH, CY, CZ          |                     |
|      |                   |          |          |                 | LU, MC, NL, PT, RO          |                     |
|      |                   |          |          |                 | GN, GQ, GW, ML, MR          |                     |
|      | US 200322908      |          |          | 20031211        | US 2002-153154              | 20020521            |
|      | EP 1507536        |          | A2       | 20050223        | EP 2003-724272              | 20030423            |
|      |                   |          |          |                 | GB, GR, IT, LI, LU          |                     |
|      | IE,               | SI, LT,  | LV, FI,  | RO, MK,         | CY, AL, TR, BG, CZ          | EE, HU, SK          |
|      |                   |          |          | 20040708        | US 2003-735506              | 20031211            |
| PRIC | RITY APPLN. I     | NFO.:    |          |                 | US 2002-153154              | A 20020521          |
|      |                   |          |          |                 | WO 2003-US13057             | W 20030423          |
| AB   |                   |          |          |                 | the long-term relie         | ef of chronic       |
|      | _                 | -        | •        | _               | the subject an              |                     |
|      |                   |          |          |                 | the absence of              |                     |
|      |                   |          |          |                 | iod of at least thre        |                     |
|      |                   |          |          |                 | tained in the absend        |                     |
|      |                   |          |          |                 | or. The <b>analgesic</b> of |                     |
|      | adrenergic r      | eceptor  | can be,  | for exam        | mple, the $lpha$ -2B recep  | otor.               |
| ΙT   | 366786-91-6       | 629628-3 | 15-5     |                 |                             |                     |
|      |                   |          |          |                 | THU (Therapeutic us         | se); BIOL           |
|      | (Biological       | study);  | USES (U  | Jses)           |                             |                     |
|      | $(\alpha$ - adren | oceptor  | activat  | tion for a      | alleviating <b>pain</b>     | •                   |
|      | )                 |          |          |                 |                             |                     |
| RN   | 366786-91-6       |          | _        |                 |                             |                     |
| CN   | Thiourea, N-      | [(3-chlo | oro-2-fl | luoropheny      | yl)methyl]-N'-(2-hyd        | lroxyethyl) - (9CI) |
|      | (CA INDEX NA      | ME)      |          |                 |                             |                     |

$$C1$$
  $CH_2-NH-C-NH-CH_2-CH_2-OH$ 

RN 629628-15-5 HCAPLUS

CN Thiourea, N-[(2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

Me 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

L19 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2003:334962 HCAPLUS

DOCUMENT NUMBER:

138:331737

TITLE:

Methods and compositions for modulating  $\alpha$  adrenergic receptor activity, and therapeutic

use thereof

INVENTOR(S):

Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken; Garst,

Michael E.; Wheeler, Larry A.

PATENT ASSIGNEE(S): SOURCE:

Allergan, Inc., USA PCT Int. Appl., 35 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PAT                    | ENT I | . O <i>l</i> | ,   | ,         | KIN | D    | DATE               |               |       | APPL  | ICAT: | ION I | NO.      |          | D    | ATE |     |
|------------------------|-------|--------------|-----|-----------|-----|------|--------------------|---------------|-------|-------|-------|-------|----------|----------|------|-----|-----|
|                        |       |              |     |           |     | _    |                    |               |       |       |       |       |          |          | _    |     |     |
| · WO 2003035178        |       |              | A1  | A1 200    |     |      | 0030501 WO 2002-US |               |       |       | 571   |       | 20021011 |          |      |     |     |
|                        | W:    | ΑE,          | AG, | AL,       | AM, | ΑT,  | AU,                | ΑZ,           | BA,   | BB,   | BG,   | BR,   | BY,      | ΒZ,      | CA,  | CH, | CN, |
|                        |       | CO,          | CR, | CU,       | CZ, | DE,  | DK,                | DM,           | DZ,   | EC,   | EE,   | ES,   | FI,      | GB,      | GD,  | GE, | GH, |
|                        |       | GM,          | HR, | HU,       | ID, | IL,  | IN,                | ıs,           | JΡ,   | KE,   | KG,   | KΡ,   | KR,      | ΚZ,      | LC,  | LK, | LR, |
|                        |       | LS,          | LT, | LU,       | LV, | MA,  | MD,                | MG,           | MK,   | MN,   | MW,   | MX,   | MZ,      | NO,      | NZ,  | OM, | PH, |
|                        |       | PL,          | PT, | RO,       | RU, | SD,  | SE,                | SG,           | SI,   | SK,   | SL,   | ТJ,   | TM,      | TN,      | TR,  | TT, | TZ, |
|                        |       | UΑ,          | ŪĠ, | UΖ,       | VN, | YU,  | ZA,                | ZM,           | zw    |       |       |       |          |          | •    |     |     |
|                        | RW:   | GH,          | GM, | ΚE,       | LS, | MW,  | ΜZ,                | SD,           | SL,   | SZ,   | TZ,   | ŪĠ,   | ZM,      | ZW,      | AM,  | AZ, | BY, |
|                        |       | KG,          | ΚZ, | MD,       | RU, | ТJ,  | TM,                | ΑT,           | ΒE,   | BG,   | CH,   | CY,   | CZ,      | DE,      | DK,  | EE, | ES, |
|                        |       | FI,          | FR, | GB,       | GR, | ΙE,  | ΙT,                | LU,           | МC,   | NL,   | PT,   | SE,   | SK,      | TR,      | BF,  | ВJ, | CF, |
|                        |       | CG,          | CI, | CM,       | GA, | GN,  | GQ,                | GW,           | ML,   | MR,   | NE,   | SN,   | TD,      | TG       |      |     |     |
| US 2003092766          |       |              |     | <b>A1</b> |     | 2003 | 0515               | US 2001-39827 |       |       |       |       |          | 20011019 |      |     |     |
| PRIORITY APPLN. INFO.: |       |              |     |           |     |      |                    | 1             | US 20 | 001-3 | 3982  | 7     | 1        | A 20     | 0011 | 119 |     |
| OTHER SO               | URCE  | (S):         |     |           | MAR | PAT  | 138:               | 3317          | 37    |       |       |       |          |          |      |     |     |

AB Methods and compns. are discloses for the treatment of pain and intraocular pressure. Particularly disclosed are compns. for the treatment of chronic pain, glaucoma, and methods for their use.

Ι

Compds. of the invention include e.g. I (preparation given).

IT 61290-32-2P 366786-91-6P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(thiourea derivs., preparation and use in treatment of glaucoma and pain)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ &$$

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thiourea derivs., prepn. and use in treatment of glaucoma and pain

REFERENCE COUNT:

4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2002:675989 HCAPLUS

DOCUMENT NUMBER:

137:216704

TITLE:

2-Hydroxyethylthioureas useful as modulators of

α2B adrenergic receptors

INVENTOR (S):

Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken; Garst,

Michael E.

PATENT ASSIGNEE(S):

Allergan Sales, Inc., USA; Allergan, Inc.

SOURCE:

PCT Int. Appl., 75 pp.

DOCUMENT TYPE:

CODEN: PIXXD2

LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

| PATENT NO.                      | KIND         | DATE                      | APPLICATION NO.       | DATE           |
|---------------------------------|--------------|---------------------------|-----------------------|----------------|
| WO 2002068384                   | A2           | 20020906                  | WO 2002-US5021        | 20020219       |
| WO 2002068384<br>W: AE, AG, AL, | A3<br>AM, AT | 20030306<br>'.`AU. AZ. BA | A. BB. BG. BR. BY. BZ | Z. CA. CH. CN. |

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CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
                GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
                PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ,
                                                                                            ŤЈ,
           RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
                BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
      US 2002161051
                                 A1
                                         20021031
                                                        US 2001-794874
                                                                                     20010227
      US 6534542
                                 B2
                                         20030318
      CA 2439838
                                 AA
                                         20020906
                                                        CA 2002-2439838
                                                                                     20020219
      EP 1381593
                                 A2
                                         20040121
                                                        EP 2002-707824
                                                                                     20020219
               AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
                IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
      JP 2004524312
                                         20040812
                                                        JP 2002-567898
                                 T2
                                                                                     20020219
PRIORITY APPLN. INFO.:
                                                        US 2001-794874
                                                                                 Α
                                                                                     20010227
                                                        WO 2002-US5021
                                                                                 W
                                                                                     20020219
OTHER SOURCE(S):
                               MARPAT 137:216704
GΙ
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AB

CN

Thioureas I [X = (un) substituted CH2, CH2CH2, CH2CH2CH2; X1 = bond, CH2; R-R2 = H, alkyl, alkenyl, alkynyl, OH, alkoxy, acyloxy, F, Cl, Br, I; R3 = H, acyl] and their ring-unsatd. analogs were prepared I specifically or selectively modulate α2B and/or α2C adrenergic receptors in preference over α2A adrenergic receptors and are useful for alleviating chronic pain and allodynia with no or only minimal cardiovascular and/or sedative side-effects. Thus, 3-cyclohexene-1-carboxaldehyde was reduced to the alc., which was mesylated, converted to azide, and treated with CS2 and HOCH2CH2NH2 to give 1-(1-cyclohexen-4-yl)methyl-3-(2-hydroxyethyl)thiourea (II). II had EC50 17 nM in the RSAT test. 455255-92-2P 455255-94-4P 455255-95-5P 455255-98-8P 455255-99-9P 455256-00-5P 455256-01-6P 455256-08-3P 455256-09-4P 455256-10-7P 455256-11-8P 455256-12-9P 455256-13-0P 455256-14-1P 455256-15-2P 455256-16-3P 455256-17-4P 455256-18-5P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (preparation of 2-hydroxyethylthioureas useful as modulators of  $\alpha 2B$ adrenergic receptors) RN455255-92-2 HCAPLUS

Thiourea, N-(cyclohexylmethyl)-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 455255-94-4 HCAPLUS

CN Thiourea, N-(1-cyclohexen-1-ylmethyl)-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 455255-95-5 HCAPLUS

CN Thiourea, N-(2-cyclohexen-1-ylmethyl)-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 455255-98-8 HCAPLUS

CN Thiourea, N-(3-cyclohexen-1-ylmethyl)-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 455255-99-9 HCAPLUS

CN Thiourea, N-(cyclopentylmethyl)-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\sim$$
 CH<sub>2</sub>- NH- C- NH- CH<sub>2</sub>- CH<sub>2</sub>- ОН

RN 455256-00-5 HCAPLUS

CN Thiourea, N-(cycloheptylmethyl)-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 455256-01-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(6-methyl-3-cyclohexen-1-yl)methyl](9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ \parallel & & \\ & \parallel & \\ & \text{CH}_2-\text{NH}-\text{C}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OH} \\ & & \\ & \text{Me} \end{array}$$

RN 455256-08-3 HCAPLUS

CN Thiourea, N-[(2-bromo-1-cyclohexen-1-yl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel & \\ & \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \\ & & \text{Br} \end{array}$$

RN 455256-09-4 HCAPLUS

CN Thiourea, N-[(3-ethyl-2-cyclohexen-1-yl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 455256-10-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-methyl-2-cyclohexen-1-yl)methyl](9CI) (CA INDEX NAME)

RN 455256-11-8 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2-methyl-2-cyclohexen-1-yl)methyl]-(9CI) (CA INDEX NAME)

RN 455256-12-9 HCAPLUS

CN Thiourea, N-[(2-ethyl-2-cyclohexen-1-yl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 455256-13-0 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2-methyl-1-cyclohexen-1-yl)methyl]-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel & \\ & \text{CH}_2\text{--}\text{NH--}\text{C--}\text{NH--}\text{CH}_2\text{--}\text{CH}_2\text{--}\text{OH} \\ \\ & & \text{Me} \end{array}$$

RN 455256-14-1 HCAPLUS

CN Thiourea, N-[(2-ethyl-1-cyclohexen-1-yl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN455256-15-2 HCAPLUS

CNThiourea, N-[(2-butyl-1-cyclopenten-1-yl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

455256-16-3 HCAPLUS RN

Thiourea, N-[(2-butyl-2-cyclopenten-1-yl)methyl]-N'-(2-hydroxyethyl)-CN (9CI) (CA INDEX NAME)

RN 455256-17-4 HCAPLUS

Thiourea, N-(2-hydroxyethyl)-N'-[(2-methyl-1-cyclopenten-1-yl)methyl]-CN (9CI) (CA INDEX NAME)

RN 455256-18-5 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-methyl-1-cyclopenten-1-yl)methyl]-(9CI) (CA INDEX NAME)

L19 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:521523 HCAPLUS

DOCUMENT NUMBER: 137:73273

TITLE: Adrenergic receptor ligand-neurotoxin

conjugates and methods for treating pain

INVENTOR (S): Gil, Daniel W.; Aoki, Kei Roger

PATENT ASSIGNEE(S): Allergan Sales, Inc., USA SOURCE:

PCT Int. Appl., 76 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

|                                                                                                                                                 |               |      |      |             |             |       |       | APPLICATION NO. |                                   |      |               |              |          | DATE |          |          |     |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------|------|------|-------------|-------------|-------|-------|-----------------|-----------------------------------|------|---------------|--------------|----------|------|----------|----------|-----|--|--|
|                                                                                                                                                 |               |      |      | <b></b>     |             |       |       |                 |                                   |      |               |              |          |      |          |          |     |  |  |
| WO                                                                                                                                              | WO 2002053177 |      |      | A2 20020711 |             |       |       | WO 2            | 001-                              | US48 | 651           |              | 20011214 |      |          |          |     |  |  |
| WO 2002053177                                                                                                                                   |               |      |      |             | A3 2003     |       |       | 0918            |                                   |      |               |              |          |      |          |          |     |  |  |
|                                                                                                                                                 | W:            | ΑE,  | AG,  | AL,         | AM,         | AT,   | AU,   | ΑZ,             | BA,                               | BB,  | ВG,           | BR,          | BY,      | ΒZ,  | CA,      | CH,      | CN, |  |  |
|                                                                                                                                                 |               | CO,  | CR,  | CU,         | CZ,         | DE,   | DK,   | DM,             | DZ,                               | EC,  | EE,           | ES,          | FI,      | GB,  | GD,      | GE,      | GH, |  |  |
|                                                                                                                                                 |               |      |      |             |             |       |       |                 |                                   |      |               |              |          |      |          |          | LR, |  |  |
|                                                                                                                                                 |               |      |      |             |             |       | MD,   |                 |                                   |      |               |              |          |      |          |          |     |  |  |
|                                                                                                                                                 |               |      |      | -           | -           | -     | SI,   | -               |                                   | -    | -             | -            |          |      |          | •        |     |  |  |
|                                                                                                                                                 |               |      | YU,  |             |             | •     | •     | •               |                                   | ,    |               |              |          |      | ,        | ,        | ,   |  |  |
|                                                                                                                                                 | RW:           | GH,  | •    | •           |             | MW.   | MZ.   | SD.             | SL.                               | SZ.  | TZ.           | UG.          | ZM.      | ZW.  | AM.      | A7.      | BY. |  |  |
|                                                                                                                                                 |               |      |      |             |             | -     | TM,   |                 | -                                 | -    |               | -            |          | -    |          |          | •   |  |  |
|                                                                                                                                                 |               |      |      |             |             |       | NL,   |                 |                                   |      |               |              |          |      |          |          |     |  |  |
|                                                                                                                                                 |               |      |      |             |             |       | NE,   |                 |                                   |      | ,             | ,            | ,        | ,    | ,        | J,       | 0,  |  |  |
| US                                                                                                                                              | 6787          |      |      |             |             |       |       |                 |                                   |      | 000-          | 7510         | 53       |      | 2.0      | 20001229 |     |  |  |
|                                                                                                                                                 |               |      |      |             | AA 20020711 |       |       |                 | CA 2001-2433332<br>EP 2001-990212 |      |               |              |          |      | 20011214 |          |     |  |  |
|                                                                                                                                                 |               |      |      |             |             |       |       |                 |                                   |      |               |              |          |      |          |          |     |  |  |
|                                                                                                                                                 |               | AT,  |      |             |             |       |       |                 |                                   |      |               |              |          |      |          |          |     |  |  |
|                                                                                                                                                 |               |      |      |             |             |       | RO,   |                 |                                   |      |               | <b>L</b> I,  | до,      | нд,  | υμ,      | nc,      | 11, |  |  |
| US                                                                                                                                              | 2004          |      | -    | -           |             | -     |       | •               |                                   |      |               | 7914         | 2.4      |      | 20       | 2040.    | 201 |  |  |
| PRIORIT                                                                                                                                         |               |      |      |             |             |       | 20041 | 1129            |                                   |      | 000-,         |              |          |      |          |          |     |  |  |
| INTONIT                                                                                                                                         | I REE.        | LIV. | INLO | • •         |             |       |       |                 |                                   |      | 000-<br>001-1 |              |          |      |          |          |     |  |  |
| OTHER SO                                                                                                                                        | OTTOCE        | (c). |      |             | MADI        | - m v | 127.5 | 72277           |                                   | WO 2 | 001-          | J5461        | 22T      | ,    | N 21     | JOTTA    | 214 |  |  |
|                                                                                                                                                 |               |      |      |             |             |       |       |                 |                                   |      |               | <b>-</b> b - |          |      |          |          |     |  |  |
| AB Agents for treating <b>pain</b> , methods for producing the agents, and methods for treating <b>pain</b> by administration to a patient of a |               |      |      |             |             |       |       |                 |                                   |      |               |              |          |      |          |          |     |  |  |
| mei                                                                                                                                             | CHOUS         | LOL  | Lrea | zülΠC       | y pa:       | ru D  | v adr | սոու            | cra                               | cion | TO 8          | a pat        | tient    | . OÏ | а        |          |     |  |  |

AB Agents for treating pain, methods for producing the agents, and methods for treating pain by administration to a patient of a therapeutically effective amount of the agent, are disclosed. The agent may include a clostridial neurotoxin, a fragment or a derivative thereof, attached to a targeting component, wherein the targeting component is selected form a group consisting of compds. which selectively binds at the  $\alpha 2b$  or  $\alpha 2b/\alpha 2c$  adrenergic receptor subtype(s) as compared to other binding sites, e.g. the  $\alpha 2a$  adrenergic receptor subtype.

IT 61290-32-2D, conjugates 366786-91-6D, conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(adrenergic receptor ligand-neurotoxin conjugates and methods for treating pain)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & S \\ \parallel & & \parallel \\ & & \square \\ & \square \\ & & & \square \\ & \square \\$$

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
  $CH_2-NH-C-NH-CH_2-CH_2-OH$ 

L19 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2005 ACS' on STN

ACCESSION NUMBER: 2002:369027 HCAPLUS

DOCUMENT NUMBER: 136:363872

TITLE: Preparation of thiourea compounds for modulating

 $\alpha$ - adrenergic receptor activity and use

in the treatment of pain

INVENTOR(S): Chow, Ken; Gil, Daniel W.; Fang, Wenkui; Garst,

Michael E.; Wheeler, Larry A.

PATENT ASSIGNEE(S): Allergan Sales, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S.

Ser. No. 548,315, abandoned.

CODEN: USXXCO

Ι

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO.             | KIND   | DATE       | APPLICATION NO.   | DATE     |
|------------------------|--------|------------|-------------------|----------|
|                        |        |            |                   |          |
| US 2002058839          | A1     | 20020516   | US 2001-778975    | 20010205 |
| US 6545182             | B2     | 20030408   |                   |          |
| PRIORITY APPLN. INFO.: |        | ,          | US 2000-548315 B2 | 20000413 |
| OTHER SOURCE(S):       | MARPAT | 136:363872 |                   |          |
| GI                     |        |            |                   |          |

$$R^2$$
 $R^3$ 
 $R^4$ 
 $R^5$ 
 $R^5$ 
 $R^5$ 
 $R^5$ 
 $R^5$ 

Methods and compns. are disclosed which use thiourea compds. I (R1, R5 = halo, alkyl, alkoxy, etc.; R2, R4 = halo, alkyl, alkoxy, etc.; R3 = F, H), and alkyl esters thereof, for the treatment of pain. Preparation of I [R1 = F; R2 = Cl; R3-R5 = H] which showed EC50 of 16 nM and 457 nM at  $\alpha$ 2B and  $\alpha$ 2C receptor in RSAT assay, was given. Particularly disclosed are compns. for the treatment of chronic pain, and methods for their use.

IT 61290-32-2P 61290-44-6P 61290-46-8P 61290-47-9P 74548-54-2P 74787-66-9P 366786-78-9P 366786-79-0P 366786-80-3P 366786-81-4P 366786-82-5P 366786-83-6P 366786-84-7P 366786-85-8P 366786-86-9P 366786-87-0P 366786-89-2P 366786-90-5P

366786-91-6P 366786-92-7P 366786-93-8P 366786-94-9P 366786-95-0P 366786-96-1P 366786-97-2P 366786-98-3P 366786-99-4P 366787-00-0P 366787-01-1P 366787-02-2P 366787-03-3P 366787-04-4P 366787-05-5P 366787-06-6P 366787-07-7P 366787-09-9P 366787-10-2P 366787-11-3P 366787-12-4P 366787-13-5P 366787-14-6P 366787-15-7P 366787-16-8P 366787-17-9P 366787-18-0P 366787-19-1P 366787-20-4P 366787-21-5P 366787-22-6P 366787-23-7P 366787-24-8P 366787-25-9P 366787-27-1P 366787-28-2P 366787-29-3P 366787-30-6P 366787-31-7P 366787-32-8P 366787-33-9P 366787-34-0P 366787-35-1P 366787-36-2P 366787-37-3P 366787-38-4P 366787-39-5P 366787-40-8P 366787-41-9P 366787-42-0P 366787-43-1P 366787-45-3P 366787-46-4P 366787-47-5P 366787-48-6P 366787-49-7P 366787-50-0P 366787-51-1P 366787-52-2P 366787-53-3P 366787-54-4P 366787-55-5P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of thiourea compds. for modulating  $\alpha$ - adrenergic receptor activity and use in treatment of pain) 61290-32-2 HCAPLUS Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c} \mathtt{S} \\ \parallel \\ \mathtt{CH_2-NH-C-NH-CH_2-CH_2-OH} \end{array}$$

RN

CN

RN 61290-44-6 HCAPLUS
CN Thiourea, N-[(2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 61290-46-8 HCAPLUS
CN Thiourea, N-(2-hydroxyethyl)-N'-[[2-(trifluoromethyl)phenyl]methyl]- (9CI)
(CA INDEX NAME)

RN 61290-47-9 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[[3-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

RN 74548-54-2 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2-methylphenyl)methyl]- (9CI) (CA INDEX NAME)

RN 74787-66-9 HCAPLUS

CN Thiourea, N-[(4-bromophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-78-9 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4,6-tetrafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & S \\ \parallel & & \parallel \\ & & \square \\ & \square \\ & &$$

RN 366786-79-0 HCAPLUS

CN Thiourea, N-[(2-fluoro-6-iodophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-80-3 HCAPLUS

CN Thiourea, N-[(2,6-dichlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
 $CH_2-NH-C-NH-CH_2-CH_2-OH$ 
 $C1$ 

RN 366786-81-4 HCAPLUS

CN Thiourea, N-[(2,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-82-5 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[[3-(trifluoromethoxy)phenyl]methyl](9CI) (CA INDEX NAME)

RN 366786-83-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)

$$\label{eq:ch2-nh-ch2-ch2-oh} \texttt{Me} \underbrace{\qquad \qquad \qquad }_{\texttt{CH}_2-\,\texttt{NH}-\,\texttt{C}-\,\texttt{NH}-\,\texttt{CH}_2-\,\texttt{CH}_2-\,\texttt{OH}}^{\texttt{S}}$$

RN 366786-84-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(4-methylphenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366786-85-8 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366786-86-9 HCAPLUS

CN Thiourea, N-[(3-chloro-4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel \\ & \square \\ & \square \\ & & \square \\$$

RN 366786-87-0 HCAPLUS

CN Thiourea, N-[(2-ethoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-89-2 HCAPLUS

CN Thiourea, N-[(2-chloro-4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-90-5 HCAPLUS

CN Thiourea, N-[(2-chloro-6-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-92-7 HCAPLUS

CN Thiourea, N-[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$F_3C$$
  $CH_2-NH-C-NH-CH_2-CH_2-OH$ 

RN 366786-93-8 HCAPLUS

CN Thiourea, N-[(2-bromophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-94-9 HCAPLUS

CN Thiourea, N-[(3-bromophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{S} & & \\ \parallel & \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{C} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \end{array}$$

RN 366786-95-0 HCAPLUS

CN Thiourea, N-[(3-chlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

C1 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-96-1 HCAPLUS

CN Thiourea, N-[(2,3-dichlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \text{C1} & \text{S} \\ & \text{CH}_2-\text{NH}-\text{C}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OH} \\ \end{array}$$

RN 366786-97-2 HCAPLUS

CN Thiourea, N-[(2,3-difluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-98-3 HCAPLUS

CN Thiourea, N-[(3-bromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel & \\ & \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \end{array}$$

RN 366786-99-4 HCAPLUS

CN Thiourea, N-[(3-chloro-2,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & & \\ \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ & & \\ & & \\ & & \\ \end{array}$$

RN 366787-00-0 HCAPLUS

CN Thiourea, N-[(5-chloro-2-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX:NAME)

OMe 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-01-1 HCAPLUS

CN Thiourea, N-[(3-fluoro-2-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathsf{OMe} & \mathsf{S} \\ \parallel \\ \mathsf{CH}_2 - \mathsf{NH} - \mathsf{C} - \mathsf{NH} - \mathsf{CH}_2 - \mathsf{CH}_2 - \mathsf{OH} \end{array}$$

RN 366787-02-2 HCAPLUS

CN Thiourea, N-[(5-bromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-03-3 HCAPLUS

CN Thiourea, N-[(2-bromo-5-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-04-4 HCAPLUS

CN Thiourea, N-[(2-fluoro-3-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

MeO 
$$CH_2 - NH - C - NH - CH_2 - CH_2 - OH$$

RN 366787-05-5 HCAPLUS

CN Thiourea, N-[(2-fluoro-5-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

RN 366787-06-6 HCAPLUS

CN Thiourea, N-[(2-fluoro-5-methylphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-07-7 HCAPLUS

CN Thiourea, N-[(3-bromo-2,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{F} & \mathbf{S} \\ \parallel \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{C} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \\ \mathbf{F} \end{array}$$

RN 366787-09-9 HCAPLUS

CN Thiourea, N-[(5-chloro-2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-10-2 HCAPLUS

CN Thiourea, N-[(5-bromo-2-chlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-11-3 HCAPLUS

CN Thiourea, N-[(2-bromo-5-chlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

RN 366787-12-4 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,4,5-trifluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & \\ F & & \\ & & \\ F & & \\ \end{array}$$

RN 366787-13-5 HCAPLUS

CN Thiourea, N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-14-6 HCAPLUS

CN Thiourea, N-[(3,5-dichloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

C1 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-15-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4-trifluorophenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366787-16-8 HCAPLUS

CN Thiourea, N-[(3-chloro-2,4,6-trifluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\$$

RN 366787-17-9 HCAPLUS

CN Thiourea, N-[(6-bromo-2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

Me 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-18-0 HCAPLUS

CN Thiourea, N-[(3-bromo-2-fluoro-5-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-19-1 HCAPLUS

CN Thiourea, N-[(5-bromo-2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{S} & \parallel \\ \mathbf{C}\mathbf{H}_2 - \mathbf{N}\mathbf{H} - \mathbf{C} - \mathbf{N}\mathbf{H} - \mathbf{C}\mathbf{H}_2 - \mathbf{C}\mathbf{H}_2 - \mathbf{O}\mathbf{H} \\ \hline \\ \mathbf{F} & \mathbf{M}\mathbf{e} \end{array}$$

RN 366787-20-4 HCAPLUS

CN Thiourea, N-[(3,5-dibromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-21-5 HCAPLUS

CN Thiourea, N-[(5-bromo-2,3,4-trifluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & S \\ \parallel & & \parallel \\ & & \parallel \\ & & \downarrow \\ &$$

RN 366787-22-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4-trifluoro-5-methylphenyl)methyl]-(9CI) (CA INDEX NAME)

RN 366787-23-7 HCAPLUS

CN Thiourea, N-[(5-bromo-3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel & \\ & \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & & \\ & & & \\ & & \\ & & & \\ & & \\ & & & \\ & & \\ & & & \\ & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 366787-24-8 HCAPLUS

CN Thiourea, N-[(3-bromo-2-fluoro-6-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

Br 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-25-9 HCAPLUS

CN Thiourea, N-[(5-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-27-1 HCAPLUS

CN Thiourea, N-[(2-chloro-3,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

RN 366787-28-2 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2-iodophenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366787-29-3 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-iodophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{S} & \\ \parallel & \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \end{array}$$

RN 366787-30-6 HCAPLUS

CN Thiourea, N-[(2,5-difluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-31-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(pentafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \parallel & \parallel \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \hline \\ F & F \end{array}$$

RN 366787-32-8 HCAPLUS

CN Thiourea, N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-33-9 HCAPLUS

CN Thiourea, N-[(2-fluoro-6-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathsf{OMe} & \mathsf{S} \\ | \\ \mathsf{CH}_2 - \mathsf{NH} - \mathsf{C} - \mathsf{NH} - \mathsf{CH}_2 - \mathsf{CH}_2 - \mathsf{OH} \\ \\ \mathsf{F} \end{array}$$

RN 366787-34-0 HCAPLUS

CN Thiourea, N-[(5-fluoro-2-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-35-1 HCAPLUS

CN Thiourea, N-[[2-fluoro-6-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \text{CF}_3 & \text{S} \\ || \\ \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \\ \text{F} \end{array}$$

RN 366787-36-2 HCAPLUS

CN Thiourea, N-[(2,3-dichloro-6-fluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

RN 366787-37-3 HCAPLUS

CN Thiourea, N-[[2-fluoro-5-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \parallel & \parallel \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \hline \\ CF_3 & \end{array}$$

RN 366787-38-4 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluoro-5-methylphenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

RN 366787-39-5 HCAPLUS

CN Thiourea, N-[(3,6-dichloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

C1 
$$\begin{array}{c|c} S \\ \parallel \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \end{array}$$

RN 366787-40-8 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,5,6-tetrafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366787-41-9 HCAPLUS

CN Thiourea, N-[(5-fluoro-2-hydroxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME),

RN 366787-42-0 HCAPLUS

CN Thiourea, N-[(2-fluoro-3-iodophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-43-1 HCAPLUS

CN Thiourea, N-[(2-fluoro-5-iodophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-45-3 HCAPLUS

CN Thiourea, N-[(6-bromo-2-fluoro-3-iodophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{F} & \mathbf{S} \\ \parallel \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{C} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \\ \\ \mathbf{Br} & \end{array}$$

RN 366787-46-4 HCAPLUS

CN Thiourea, N-[(3-bromo-2,4-difluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & & \\ \text{Br} & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 366787-47-5 HCAPLUS

CN Thiourea, N-[(6-bromo-2,3-difluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \parallel \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \\ Br \end{array}$$

RN 366787-48-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4,5-tetrafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$F \longrightarrow F \qquad F$$

RN 366787-49-7 HCAPLUS

CN Thiourea, N-[(3,6-dibromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{F} & \mathbf{S} \\ \parallel & \parallel \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{C} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \\ \\ \mathbf{Br} & \mathbf{Br} \end{array}$$

RN 366787-50-0 HCAPLUS

CN Thiourea, N-[(2,3-dibromo-5,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-51-1 HCAPLUS

CN Thiourea, N-[(2-bromo-6-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

RN 366787-52-2 HCAPLUS

CN Thiourea, N-[[2,5-bis(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-53-3 HCAPLUS

CN Thiourea, N-[(2,5-dimethoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-54-4 HCAPLUS

CN Thiourea, N-[[2-chloro-5-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-55-5 HCAPLUS

CN Thiourea, N-[(2,3-dimethoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \text{OMe} & \text{S} \\ | \\ | \\ \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \end{array}$$

L19 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2001:780662 HCAPLUS

DOCUMENT NUMBER:

135:327361

TITLE:

Methods and compositions using benzylthiourea derivatives for modulating alpha adrenergic

receptor activity

INVENTOR(S):

Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken; Garst,

Michael E.; Wheeler, Larry A.

PATENT ASSIGNEE(S): SOURCE:

Allergan Sales, Inc., USA

PCT Int. Appl., 28 pp.

CODEN: PIXXD2

DOCUMENT TYPE: LANGUAGE:

Patent English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

| PATI                   | KINI          | D   | DATE |             |             | APPLICATION NO. |          |                |                 |       | DATE   |       |          |          |      |     |     |  |
|------------------------|---------------|-----|------|-------------|-------------|-----------------|----------|----------------|-----------------|-------|--------|-------|----------|----------|------|-----|-----|--|
|                        |               |     |      |             |             |                 |          |                |                 |       |        |       |          |          |      |     |     |  |
| WO 2                   | O 2001078703  |     |      |             |             |                 | 20011025 |                | WO 2001-US11843 |       |        |       |          | 20010411 |      |     |     |  |
| WO 2                   | WO 2001078703 |     |      |             |             | A3 20020        |          |                | 1               |       |        |       |          |          |      |     |     |  |
|                        | W: A          | Æ,  | AG,  | AL,         | AM,         | AT,             | ΑU,      | ΑZ,            | BA,             | BB,   | , BG,  | BR,   | BY,      | ΒZ,      | CA,  | CH, | CN, |  |
|                        | C             | CR, | CU,  | CZ,         | DE,         | DK,             | DM,      | DZ,            | ΕE,             | ES,   | FI,    | GB,   | GD,      | GE,      | GH,  | GM, | HR, |  |
|                        | H             | IU, | ID,  | IL,         | IN,         | IS,             | JP,      | KE,            | KG,             | KP,   | KR,    | ΚZ,   | LC,      | LK,      | LR,  | LS, | LT, |  |
|                        | I             | υ,  | LV,  | MA,         | MD,         | MG,             | MK,      | MN,            | MW,             | MX,   | MZ,    | NO,   | NZ,      | PL,      | PT,  | RO, | RU, |  |
|                        | S             | SD, | SE,  | SG,         | SI,         | SK,             | SL,      | ТJ,            | TM,             | TR,   | TT,    | TZ,   | UA,      | UG,      | UZ,  | VN, | YU, |  |
|                        | 2             | ZA, | ZW,  | AM,         | ΑZ,         | BY,             | KG,      | ΚZ,            | MD,             | RU,   | TJ,    | TM .  |          |          |      |     |     |  |
|                        | RW: C         | H,  | GM,  | KE,         | LS,         | MW,             | MZ,      | SD,            | SL,             | SZ,   | TZ,    | UG,   | ZW,      | AT,      | BE,  | CH, | CY, |  |
|                        | Ι             | E,  | DK,  | ES,         | FI,         | FR,             | GB,      | GR,            | ΙE,             | IT,   | LU,    | MC,   | NL,      | PT,      | SE,  | TR, | BF, |  |
|                        | E             | IJ, | CF,  | CG,         | CI,         | CM,             | GΑ,      | GN,            | GW,             | ML,   | MR,    | NE,   | SN,      | TD,      | TG   |     |     |  |
| US 6313172             |               |     |      |             | B1 20011106 |                 |          |                |                 | US 2  | 2000-  | 5484  | 20000413 |          |      |     |     |  |
| CA 2                   | CA 2406057    |     |      |             |             | AA 20011025     |          |                |                 | CA 2  | 2001-  | 2406  | 20010411 |          |      |     |     |  |
| EP 1280525             |               |     |      |             | A2 20030205 |                 |          |                |                 | EP 2  | 2001-  | 9268  | 20010411 |          |      |     |     |  |
| EP 1280525             |               |     |      | B1 20050209 |             |                 |          |                |                 |       |        |       |          |          |      |     |     |  |
|                        | R: A          | Т,  | ΒE,  | CH,         | DE,         | DK,             | ES,      | FR,            | GB,             | GR,   | IT,    | LI,   | LU,      | NL,      | SE,  | MC, | PT, |  |
|                        | I             | Ε,  | SI,  | LT,         | LV,         | FI,             | RO,      | MK,            | CY,             | AL,   | TR     |       |          |          |      |     |     |  |
|                        |               |     |      |             |             |                 |          |                | JP 2001-576004  |       |        |       |          |          |      |     |     |  |
| NZ 522027              |               |     |      |             | A 20041126  |                 |          | NZ 2001-522027 |                 |       |        |       | 20010411 |          |      |     |     |  |
| PRIORITY APPLN. INFO.: |               |     |      |             |             |                 |          | •              | US 2            | 2000- | 5484   | 10    | 7        | A 20     | 0000 | 413 |     |  |
|                        |               |     |      |             |             |                 |          |                | 1               | WO 2  | 2001-1 | JS118 | 343      | 1        | W 2  | 010 | 411 |  |
| OTHER SOURCE(S):<br>GI |               |     |      |             | MARI        | PAT             | 135:     | 32736          | 51              |       |        |       |          |          |      |     |     |  |

Ι

- AB The invention discloses benzylthiourea derivs. I (R1, R3 = F, H; R2 = C1, H; with provisos, and alkyl esters thereof) as  $\alpha 2$  adrenergic receptor modulators. The invention also describes the synthesis of a compound II (wherein R1= H, R2= Cl and R3 = F). The effects of these disclosed compds. on acute and chronic pain, their sedative action and their cardiovascular effects are described.
- IT 61290-32-2P 61290-44-6P 366786-91-6P

  RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(benzylthiourea derivs. for modulating alpha adrenoceptor

activity and their application in pain therapy)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 61290-44-6 HCAPLUS

CN Thiourea, N-[(2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

IT 61290-32-2D, alkyl esters 366786-91-6D, alkyl esters
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(benzylthiourea derivs. for modulating alpha adrenoceptor activity and their application in pain therapy)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2 - NH - C - NH - CH_2 - CH_2 - OH$$

RN 366786-91-6 HCAPLUS Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) CN (CA INDEX NAME)

L19 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

2001:780661 HCAPLUS

DOCUMENT NUMBER:

135:298811

TITLE:

Thiourea compounds for modulating  $\alpha$ -

adrenergic receptor activity, preparation,

compositions, and use in the treatment of pain

INVENTOR(S):

Chow, Ken; Gil, Daniel W.; Fang, Wenkui Ken; Garst,

Michael E.; Wheeler, Larry A.

PATENT ASSIGNEE(S):

SOURCE:

Allergan Sales, Inc., USA

PCT Int. Appl., 41 pp.

CODEN: PIXXD2 Patent

DOCUMENT TYPE:

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

| PATENT NO.             |            |             |     |             |             | D    | DATE     |      | APPLICATION NO. |                |          |          |     |     | DATE     |      |     |  |
|------------------------|------------|-------------|-----|-------------|-------------|------|----------|------|-----------------|----------------|----------|----------|-----|-----|----------|------|-----|--|
| WO                     | 2001078702 |             |     |             | A2 20011025 |      |          | ,    | WO 2            | 001-           | US11:    | 20010411 |     |     |          |      |     |  |
| WO                     | 2001078702 |             |     | A3 20020321 |             |      |          |      |                 |                |          |          |     |     |          |      |     |  |
|                        | W:         | ΑE,         | AG, | AL,         | AM,         | AT,  | ΑU,      | ΑZ,  | BA,             | BB,            | BG,      | BR,      | BY, | ΒZ, | CA,      | CH,  | CN, |  |
|                        |            | CR,         | CU, | CZ,         | DE,         | DK,  | DM,      | DZ,  | EE,             | ES,            | FI,      | GB,      | GD, | GE, | GH,      | GM,  | HR, |  |
|                        |            |             |     |             |             |      | JP,      |      |                 |                |          |          |     |     |          |      |     |  |
|                        |            | LU,         | LV, | MA,         | MD,         | MG,  | MK,      | MN,  | MW,             | MX,            | MZ,      | NO,      | NZ, | PL, | PT,      | RO,  | RU, |  |
| •                      |            |             |     |             |             |      | SL,      |      |                 |                |          |          |     |     |          |      |     |  |
|                        |            | ZA,         | ZW, | AM,         | AZ,         | BY,  | KG,      | KZ,  | MD,             | RU,            | TJ,      | TM       | •   | •   | •        | •    | •   |  |
|                        | RW:        |             |     |             |             |      | MZ,      |      | •               | -              |          |          | ZW, | AT, | BE,      | CH,  | CY, |  |
|                        |            |             |     |             |             |      | GB,      |      |                 |                |          |          |     |     |          |      |     |  |
|                        |            |             |     |             |             |      | GA,      |      |                 |                |          |          |     |     |          |      | •   |  |
| CA                     | 2405       | AA 20011025 |     |             |             |      | CA 2     | 001- | 2405            | •              | 20010411 |          |     |     |          |      |     |  |
| EP                     | 1280       | A2 20030205 |     |             |             | EP 2 | 001-     | 9268 |                 | 20010411       |          |          |     |     |          |      |     |  |
|                        | R:         | AT,         | BE, | CH,         | DE,         | DK,  | ES,      | FR,  | GB,             | GR,            | IT,      | LI,      | LU, | NL, | SE,      | MC,  | PT, |  |
|                        |            |             |     |             |             |      | RO,      |      |                 |                |          | •        | •   | •   | •        | •    | •   |  |
| JP 2003530429          |            |             |     |             | T2          | ·    | 20031014 |      |                 | JP 2001-576003 |          |          |     |     | 20010411 |      |     |  |
| PRIORITY APPLN. INFO.: |            |             |     |             |             |      |          |      |                 | US 2           |          |          |     |     |          | 0000 |     |  |
|                        |            |             |     |             |             |      |          |      | 1               | WO 2           | 001-1    | JS11     | 842 | 1   | W 2      | 0010 | 411 |  |

OTHER SOURCE(S):

MARPAT 135:298811

GI

$$R^2$$
 $R^3$ 
 $R^4$ 
 $R^5$ 
 $R^5$ 
 $R^4$ 
 $R^5$ 

AB Methods and compns. are disclosed which use thiourea compds. I (R1, R2, R4, R5 = H, OH, C1-3 alkyl, etc.; R3 = H, F), and alkyl esters thereof, for the treatment of pain. Particularly disclosed are compns. for the treatment of chronic pain, and methods for their use.

IT 61290-44-6

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(thiourea compds. for modulating  $\alpha$ - adrenergic receptor

activity, preparation, compns., and use in treatment of pain)

RN 61290-44-6 HCAPLUS

CN Thiourea, N-[(2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c}
 & S \\
 & \parallel \\
 & CH_2-NH-C-NH-CH_2-CH_2-OH \\
\hline
 & F
\end{array}$$

IT 61290-32-2 61290-46-8 61290-47-9 74548-54-2 74787-66-9 366786-78-9 366786-79-0 366786-80-3 366786-81-4 366786-82-5 366786-83-6 366786-84-7 366786-85-8 366786-86-9 366786-87-0 366786-89-2 366786-90-5 366786-91-6 366786-92-7 366786-93-8 366786-94-9 366786-95-0 366786-96-1 366786-97-2 366786-98-3 366786-99-4 366787-00-0 366787-01-1 366787-02-2 366787-03-3 366787-04-4 366787-05-5 366787-06-6 366787-07-7 366787-09-9 366787-10-2 366787-11-3 366787-12-4 366787-13-5 366787-14-6 366787-15-7 366787-16-8 366787-17-9 366787-18-0 366787-19-1 366787-20-4 366787-21-5 366787-22-6 366787-23-7 366787-24-8 366787-25-9 366787-27-1 366787-28-2 366787-29-3 366787-30-6 366787-31-7 366787-32-8 366787-33-9 366787-34-0 366787-35-1 366787-36-2 366787-37-3 366787-38-4 366787-39-5 366787-40-8 366787-41-9 366787-42-0 366787-43-1 366787-45-3

366787-46-4 366787-47-5 366787-48-6

366787-49-7 366787-50-0 366787-51-1

366787-52-2 366787-53-3 366787-54-4

366787-55-5

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(thiourea compds. for modulating  $\alpha$ - adrenergic receptor activity, preparation, compns., and use in treatment of pain)

RN 61290-32-2 HCAPLUS

CN Thiourea, N-[(4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 61290-46-8 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[[2-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

RN 61290-47-9 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[[3-(trifluoromethyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

RN 74548-54-2 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2-methylphenyl)methyl]- (9CI) (CA INDEX NAME)

RN 74787-66-9 HCAPLUS

CN Thiourea, N-[(4-bromophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-78-9 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4,6-tetrafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \hline \\ F & \\ \hline \\ F & \\ \end{array} \\ \begin{array}{c|c} S \\ \hline \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \hline \\ \end{array}$$

RN 366786-79-0 HCAPLUS

CN Thiourea, N-[(2-fluoro-6-iodophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366786-80-3 HCAPLUS

CN Thiourea, N-[(2,6-dichlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-81-4 HCAPLUS

CN Thiourea, N-[(2,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & | & \\ & | & \\ & CH_2-NH-C-NH-CH_2-CH_2-OH \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ \end{array}$$

RN 366786-82-5 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[[3-(trifluoromethoxy)phenyl]methyl](9CI) (CA INDEX NAME)

RN 366786-83-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-methylphenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366786-84-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(4-methylphenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel & \\ & \parallel & \\ & \text{CH}_2-\text{NH}-\text{C}-\text{NH}-\text{CH}_2-\text{CH}_2-\text{OH} \end{array}$$

RN 366786-85-8 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{picture}(20,10) \put(0,0){\line(1,0){100}} \put(0,0){\line(1,0){10$$

RN 366786-86-9 HCAPLUS

CN Thiourea, N-[(3-chloro-4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-87-0 HCAPLUS

CN Thiourea, N-[(2-ethoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{tabular}{c|c} S \\ || \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \hline \end{tabular}$$

RN 366786-89-2 HCAPLUS

CN Thiourea, N-[(2-chloro-4-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$C1$$
  $CH_2-NH-C-NH-CH_2-CH_2-OH$ 

RN 366786-90-5 HCAPLUS

CN Thiourea, N-[(2-chloro-6-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI)
(CA INDEX NAME)

$$\begin{array}{c|c} \text{C1} & \text{S} \\ | \\ \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \\ \text{F} \end{array}$$

RN 366786-91-6 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-92-7 HCAPLUS

CN Thiourea, N-[[2-fluoro-3-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-93-8 HCAPLUS

CN Thiourea, N-[(2-bromophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & \text{S} \\ \parallel & & \parallel \\ & \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \\ & & \text{Br} \end{array}$$

RN 366786-94-9 HCAPLUS

CN Thiourea, N-[(3-bromophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-95-0 HCAPLUS

CN Thiourea, N-[(3-chlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-96-1 HCAPLUS

CN Thiourea, N-[(2,3-dichlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-97-2 HCAPLUS

CN Thiourea, N-[(2,3-difluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-98-3 HCAPLUS

CN Thiourea, N-[(3-bromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366786-99-4 HCAPLUS

CN Thiourea, N-[(3-chloro-2,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & | \\ & \\ \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ & & \\ & & \\ \end{array}$$

RN 366787-00-0 HCAPLUS

CN Thiourea, N-[(5-chloro-2-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-01-1 HCAPLUS

CN Thiourea, N-[(3-fluoro-2-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathsf{OMe} & \mathsf{S} \\ \parallel \\ \mathsf{CH}_2 - \mathsf{NH} - \mathsf{C} - \mathsf{NH} - \mathsf{CH}_2 - \mathsf{CH}_2 - \mathsf{OH} \end{array}$$

RN 366787-02-2 HCAPLUS

CN Thiourea, N-[(5-bromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-03-3 HCAPLUS

CN Thiourea, N-[(2-bromo-5-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-04-4 HCAPLUS

CN Thiourea, N-[(2-fluoro-3-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{F} & \mathbf{S} \\ \parallel \\ \mathbf{CH_2-NH-C-NH-CH_2-CH_2-OH} \end{array}$$

RN 366787-05-5 HCAPLUS

CN Thiourea, N-[(2-fluoro-5-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \hline \\ CH_2-NH-C-NH-CH_2-CH_2-OH \\ \hline \\ OMe \end{array}$$

RN 366787-06-6 HCAPLUS

CN Thiourea, N-[(2-fluoro-5-methylphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-07-7 HCAPLUS

CN Thiourea, N-[(3-bromo-2,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\$$

RN 366787-09-9 HCAPLUS

CN Thiourea, N-[(5-chloro-2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

C1 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$
 $F$ 

Me

RN 366787-10-2 HCAPLUS

CN Thiourea, N-[(5-bromo-2-chlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-11-3 HCAPLUS

CN Thiourea, N-[(2-bromo-5-chlorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-12-4 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,4,5-trifluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & \parallel & \\ & \vdash &$$

RN 366787-13-5 HCAPLUS

CN Thiourea, N-[[2-chloro-3-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-14-6 HCAPLUS

CN Thiourea, N-[(3,5-dichloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{C1} & \mathbf{S} & \mathbf{S} \\ || & \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{C} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \\ \\ \mathbf{F} & \\ \mathbf{C1} & \\ \end{array}$$

RN 366787-15-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4-trifluorophenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366787-16-8 HCAPLUS

CN Thiourea, N-[(3-chloro-2,4,6-trifluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & \parallel \\ & & \parallel \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 366787-17-9 HCAPLUS

CN Thiourea, N-[(6-bromo-2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

Me 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-18-0 HCAPLUS

CN Thiourea, N-[(3-bromo-2-fluoro-5-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

Me CH<sub>2</sub>-NH-C-NH-CH<sub>2</sub>-CH<sub>2</sub>-OH
$$F$$
Br

RN 366787-19-1 HCAPLUS

CN Thiourea, N-[(5-bromo-2-fluoro-3-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

Br 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$
F Me

RN 366787-20-4 HCAPLUS

CN Thiourea, N-[(3,5-dibromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-21-5 HCAPLUS

CN Thiourea, N-[(5-bromo-2,3,4-trifluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{S} & & \\ \parallel & \\ \mathbf{E} & \\ \mathbf{F} & \\ \mathbf{F} & \\ \mathbf{S} & \\ \parallel & \\ \mathbf{CH_2-NH-C-NH-CH_2-CH_2-OH} \end{array}$$

RN 366787-22-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4-trifluoro-5-methylphenyl)methyl]-(9CI) (CA INDEX NAME)

Me 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-23-7 HCAPLUS

CN Thiourea, N-[(5-bromo-3-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-24-8 HCAPLUS

CN Thiourea, N-[(3-bromo-2-fluoro-6-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \mathbf{F} & \mathbf{S} \\ \parallel \\ \mathbf{CH_2} - \mathbf{NH} - \mathbf{C} - \mathbf{NH} - \mathbf{CH_2} - \mathbf{CH_2} - \mathbf{OH} \\ \\ \mathbf{Me} & \end{array}$$

RN 366787-25-9 HCAPLUS

CN Thiourea, N-[(5-chloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-27-1 HCAPLUS

CN Thiourea, N-[(2-chloro-3,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$$

RN 366787-28-2 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2-iodophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & & \\ & || & & \\ & & || & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\$$

RN 366787-29-3 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(3-iodophenyl)methyl]- (9CI) (CA INDEX NAME)

RN 366787-30-6 HCAPLUS

CN Thiourea, N-[(2,5-difluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-31-7 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(pentafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \parallel & \\ \hline F & CH_2-NH-C-NH-CH_2-CH_2-OH \\ \hline \end{array}$$

RN 366787-32-8 HCAPLUS

CN Thiourea, N-[[4-fluoro-2-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CF_3$$
 $CH_2$ 
 $CH_2$ 

RN 366787-33-9 HCAPLUS

CN Thiourea, N-[(2-fluoro-6-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} \text{OMe} & \text{S} \\ | \\ \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ \\ \text{F} \end{array}$$

RN 366787-34-0 HCAPLUS

CN Thiourea, N-[(5-fluoro-2-methoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-35-1 HCAPLUS

CN Thiourea, N-[[2-fluoro-6-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

$$CF_3$$
  $S$   $||$   $CH_2-NH-C-NH-CH_2-CH_2-OH$   $F$ 

RN 366787-36-2 HCAPLUS

CN Thiourea, N-[(2,3-dichloro-6-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$C1$$
 $CH_2-NH-C-NH-CH_2-CH_2-OH$ 
 $F$ 

RN 366787-37-3 HCAPLUS

CN Thiourea, N-[[2-fluoro-5-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-38-4 HCAPLUS

CN Thiourea, N-[(3-chloro-2-fluoro-5-methylphenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

Me CH<sub>2</sub>-NH-C-NH-CH<sub>2</sub>-CH<sub>2</sub>-OH
$$F$$

RN 366787-39-5 HCAPLUS

CN Thiourea, N-[(3,6-dichloro-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

C1 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

RN 366787-40-8 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,5,6-tetrafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$F \xrightarrow[F]{F} CH_2 - NH - CH_2 - CH_2 - OH$$

RN 366787-41-9 HCAPLUS

CN Thiourea, N-[(5-fluoro-2-hydroxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-42-0 HCAPLUS

CN Thiourea, N-[(2-fluoro-3-iodophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-43-1 HCAPLUS

CN Thiourea, N-[(2-fluoro-5-iodophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-45-3 HCAPLUS

CN Thiourea, N-[(6-bromo-2-fluoro-3-iodophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ &$$

RN 366787-46-4 HCAPLUS

CN Thiourea, N-[(3-bromo-2,4-difluorophenyl)methyl]-N'-(2-hydroxyethyl)(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & \parallel \\ & & \parallel \\ & & CH_2-NH-C-NH-CH_2-CH_2-OH \end{array}$$

RN 366787-47-5 HCAPLUS

CN Thiourea, N-[(6-bromo-2,3-difluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} F & S \\ \parallel \\ \text{CH}_2\text{--} \text{NH--} \text{C---} \text{NH--} \text{CH}_2\text{---} \text{OH} \\ \\ \text{Br} \end{array}$$

RN 366787-48-6 HCAPLUS

CN Thiourea, N-(2-hydroxyethyl)-N'-[(2,3,4,5-tetrafluorophenyl)methyl]- (9CI) (CA INDEX NAME)

$$F \longrightarrow CH_2-NH-C-NH-CH_2-CH_2-OH$$

$$F \longrightarrow F$$

RN 366787-49-7 HCAPLUS

CN Thiourea, N-[(3,6-dibromo-2-fluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & & & \\ & & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\$$

RN 366787-50-0 HCAPLUS

CN Thiourea, N-[(2,3-dibromo-5,6-difluorophenyl)methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & S & \\ & \parallel & \\ & \text{CH}_2 - \text{NH} - \text{C} - \text{NH} - \text{CH}_2 - \text{CH}_2 - \text{OH} \\ & F & \\ & & F & \\ \end{array}$$

RN 366787-51-1 HCAPLUS

CN Thiourea, N-[(2-bromo-6-fluorophenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-52-2 HCAPLUS

CN Thiourea, N-[[2,5-bis(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)-(9CI) (CA INDEX NAME)

RN 366787-53-3 HCAPLUS

CN Thiourea, N-[(2,5-dimethoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

RN 366787-54-4 HCAPLUS

CN Thiourea, N-[[2-chloro-5-(trifluoromethyl)phenyl]methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

366787-55-5 HCAPLUS RN

CN Thiourea, N-[(2,3-dimethoxyphenyl)methyl]-N'-(2-hydroxyethyl)- (9CI) INDEX NAME)

MeO 
$$CH_2-NH-C-NH-CH_2-CH_2-OH$$

L19 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:

1992:6459 HCAPLUS

DOCUMENT NUMBER:

116:6459

TITLE:

Synthesis and biological activity of

2-aminothiazolines and 2-mercaptothiazolines as

octopaminergic agonists

AUTHOR (S):

CORPORATE SOURCE:

SOURCE:

Hirashima, Akinori; Yoshii, Yutaka; Eto, Morifusa Dep. Agric. Chem., Kyushu Univ., Fukuoka, 812, Japan Agricultural and Biological Chemistry (1991), 55(10),

2537-45

CODEN: ABCHA6; ISSN: 0002-1369

DOCUMENT TYPE:

LANGUAGE:

Journal English

$$R - R^1$$

AB The title compds., e.g., I (R = H, Me, Ph, Et, CH2CH2SMe; R1 = alkyl- or arylamino, SH, EtO2CCH2S) were prepared by the cyclocondensation of the corresponding isothiocyanates or CS2 with ethanolamines or their sulfates. I [R = H, R1 = 2-Me-4-ClC6H3NH (II)] was 33% as effective as octopamine at 100 µM in stimulating adenylate cyclase of Periplaneta americana ventral-nerve-cord homogenates. Its activity was nonadditive to the activity of octopamine. Stimulation of nerve-cord adenylate-cyclase activity by II was inhibited by several antagonists, including mianserin, cyproheptadine, chlorpromazine and gramine. The rank-order ability of these antagonists to block the activation by II was identical to the

rank-order ability of the same antagonists to block enzyme activation by octopamine. The  $\beta\text{-}$  adrenergic antagonist propranolol was less potent. These data suggest that II is a potent and selective agonist of octopamine-activated adenylate cyclase. Aminothiazolines, which activated adenylate cyclase by 10-87% relative to octopamine also had acaricidal activity at 300 ppm, indicating a correlation between the in vitro octopaminergic-agonist activity and in vivo acaricidal activity of aminothiazolines.

IT 6098-41-5 27803-70-9

> RL: RCT (Reactant); RACT (Reactant or reagent) (cyclocondensation of, with isothiocyanates)

RN 6098-41-5 HCAPLUS

Thiourea, N-(2-hydroxyethyl)-N'-(phenylmethyl)- (9CI) (CA INDEX NAME) CN

$$\begin{array}{c} & & S \\ || & & || \\ & \text{Ph- CH}_2\text{-- NH- C-- NH-- CH}_2\text{-- CH}_2\text{-- OH} \end{array}$$

27803-70-9 HCAPLUS RN

CN Thiourea, N-butyl-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

L19 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1987:458972 HCAPLUS

DOCUMENT NUMBER: 107:58972

TITLE: Investigations on the reaction course of diethyl

> 2-chloro-6-methylpyridine-3,5-dicarboxylate with N-amino- and N-hydroxyalkyl derivatives of thiourea

AUTHOR (S): Sladowska, H.; Bartoszko-Malik, A.; Zawisza, T.

CORPORATE SOURCE: Dep. Chem. Drugs, Sch. Med., Wroclaw, Pol.

SOURCE: Farmaco, Edizione Scientifica (1986), 41(11), 899-912

CODEN: FRPSAX; ISSN: 0430-0920

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 107:58972

Pyridopyrimidines I (R1 = Me, Ph) and pyridothiazines II (R2 = H, Me) were prepared, and they exhibited analgesic activity. The title

dinicotinate ester was heated with MeNHCSNHCH2CH2N+HEt2 Cl- in EtOH to give I (R1 = Me). IT105-81-7 3120-26-1 RL: RCT (Reactant); RACT (Reactant or reagent) (cyclocondensation reaction of, with chloronicotinic acid derivative) 105-81-7 HCAPLUS RNCN Thiourea, N-(2-hydroxyethyl)-N'-2-propenyl- (9CI) (CA INDEX NAME)  $HO-CH_2-CH_2-NH-C-NH-CH_2-CH=-CH_2$ RN3120-26-1 HCAPLUS CN Thiourea, N-(2-hydroxyethyl)-N'-methyl- (9CI) (CA INDEX NAME) MeNH-C-NH-CH2-CH2-OH L19 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN ACCESSION NUMBER: 1972:564591 HCAPLUS DOCUMENT NUMBER: 77:164591 TITLE: Benzofurans. Benzofurarylmethylimidazolines AUTHOR (S): Areschka, A.; Prost, M.; Mahaux, J. M.; Van Cromphaut, V.; Verbruggen, F.; Binon, F.; Charlier, R.; Delaunois, G.; Colot, M.; et al. CORPORATE SOURCE: Cent. Rech. S. A.-Labaz N. V., Brussels, Belg. SOURCE: Chimica Therapeutica (1972), 7(4), 337-44 CODEN: CHTPBA; ISSN: 0009-4374 DOCUMENT TYPE: Journal LANGUAGE: French GI For diagram(s), see printed CA Issue. AB Benzofuranimid-azolines including I (R = Me, Et, Ph, CHMe2, Bu), 2-(4-benzo-furyloxymethyl)imidazoline (II), 2-(7-benzofuryloxymethyl)imidazoline (III), 2-(2-ethyl-3-benzofurylmethylamino)imidazo-line (IV), 2-[2-(7-benzofuryloxy)ethylamino]imidazoline (V), and 2-(5benzofurylmethylamino)imidazoline (VI) were prepared, e.g. by formylating the benzofuran, forming the chloroalkyl and then the cyanoalkyl derivative and then the imidoic ester, which was cyclized with H2NCH2CH2NH2. I had hypertensive activity in the dog at concns. 0.1-0.2 times that of adranaline. II and III were antihypertensive in rats at 25 mg/kg. had antiinflamma-tory activity similar to that of aspirin, but no analgesic activity. 37813-05-1P RL: SPN (Synthetic preparation); PREP (Preparation) (preparation of) RN37813-05-1 HCAPLUS CN Thiourea, N-[(2-ethyl-3-benzofuranyl)methyl]-N'-(2-hydroxyethyl)- (9CI) (CA INDEX NAME)

```
Set
       Items
               Description
S1
      228763 ALPHA2 OR (ALPHA()2)
     551911 ADRENERGIC
     4273782 CONJUGAT? OR FUSION OR TARGET? OR COUPLE?
S4
    1156789 PAIN
         158 S1 AND S2 AND S3 AND S4
97 RD (unique items)
S5
S6
S7
          40
              S6 AND PY<2001
? t s7/full/25
S1
      56213
              PRAZOSIN
S2
     2280184 COUPLE? OR CONJUGATE? OR FUSION
S3
     1206888 PAIN OR NOCICEPT?
S4
        1480 S1 AND S2
S5
          16 S4 AND S3
          13 RD (unique items)
S6
      128951 NALTREXONE OR NALOXONE
S7
      315208 (ALPHA AND (ADRENERGIC)) OR ADRENOCEPT? OR
S8
ADRENORECEPT?
S9
   292865 8 (3N) (B OR C)
S10
      8241 S8 (3N) (B OR C)
S11
        140 S10 AND S7
S12
         29 S11 AND S3
        15 RD (unique items)
S13
             S7 AND S2
        2458
S14
S15
        434
             S14 AND S3
S16
        1855
             S7 (S) S2
       271 S16 (S) S3
S17
S18
        78 RD (unique items)
S19
         53 S18 AND PY<2001
        221 IMILOXAN
S20
      622 ARC239 OR (ARC()239)
56509 S20 OR S21 OR S1
S21
S22
S23 3929025 CONJUGAT? OR FUSION OR LINK? OR FUSE?
S24
         905 S22 (S) S23
S25
          10 S3 AND S24
S26
          6 RD (unique items)
        1902 S10 (5N) (AGONIST? OR ANTAGONIST?)
S27
             S23 AND S27
S28
          66
S29
          1 S28 AND S3
```